Mewburn Ellis
LLP

European Patent Attorneys
European Trade Mark Attorneys
European Design Attorneys
Chartered Patent Attorneys

York House
23 Kingsway
London WC2B 6HP

Tel +44 (0)20 7240 4405
Fax +44 (0)20 7240 9229
mail@mewburn.com

Partners
Ian Armitage
Hugh Pagat
Roger Calderbank
Patrick Stoner
Sean Walton
Nigel Hackney
Simon Kiddle
Adrian Brasnett
Roger Grimshaw*
Simon Kremer
Joanna Cripps
Robert Watson
Chris Denison
Nicholas Saltelle

Consultant
David Harrison

*not CPA or EPA

Assisted by
Sofia Aranal
Richard Clegg
Ray Coleiro
Andrew Fearnside
Graham Forrest
Michael Foster
Michael Freeman
Stephen Gill
Susan Harrison
Sheila Hill
Daniel Holt
Allan Hoyano
Juris Lyons
Matthew Naylor
Kathryn Nicholls
Stuart Nield
Alastair Rawlance
Ian Stuart
Rachel White
Wilhelmus Wytenburg

www.mewburn.com

European Patent Office
D-80298 Munich
Germany

10 June 2004

BY FACSIMILE

Dear Sirs

Opposition to European Patent No: 1 141 274 B (application no. 00902354.0)
Proprietor: ZymoGenetics, Inc.
Title: Soluble Receptor BR43x2 and Methods of Using them for Therapy
Our Ref: SJK/FG6187108

On behalf of:

Genentech, Inc.
1 DNA Way
South San Francisco
CA 94080-4990
USA

having its principal place of business in the USA,

we hereby file an **OPPOSITION** to the above numbered patent entitled "Soluble Receptor BR43x2 and Methods of Using them for Therapy".

Please charge the opposition fee of Euros 610 to our deposit account number 2805.0013 under reference 12937.

The grounds of opposition are lack of patentability (specifically lack of novelty and lack of inventive step), insufficiency of disclosure and added subject matter. All the claims of the patent are impugned and revocation of the patent in its entirety is requested. Oral proceedings are requested if the Opposition Division contemplates maintaining the patent in any form.

The details of the Opponent's case are set out in the accompanying document. Confirmation with references follow by post.

Yours faithfully

Christopher Denison
Authorised Representative
On behalf of Simon Kiddle
for MEWBURN ELLIS LLP
simon.kiddle@mewburn.com

Encs.

(To contact me personally
Please phone +44 1179 266411)

RXT/ivh

NOTICE OF OPPOSITION

to European Patent No: 1 141 274 B

of ZymoGenetics, Inc

by Genentech, Inc

1. Requests

We request revocation of the patent in its entirety under the grounds of added subject matter, lack of patentability (novelty and inventive step) and insufficiency of disclosure.

We request oral proceedings in the event that the Opposition Division forms the intention to maintain the patent in any form.

2. Cited Documents

The following references are cited in this opposition.

D1 - WO 98/39361 (St Jude Children's Research Hospital)

This application was published on 11 September 1998 and is full prior art to the patent.

D1 discloses the cloning of Transmembrane Activated CAML Interactor (TACI) protein and identify it as a TNFR family member. It is relevant to the opposed patent as claims 1 and 3 include the use of soluble polypeptides comprising the extracellular domains of TACI, and antibodies against TACI. Claim 36 of the opposed patent includes a pharmaceutical composition comprising antibodies against TACI.

D2 - WO 00/67034 (Immunex Corporation)

This application has a priority date of 30 April 1999 and a publication date of 9 November 2000. It duly entered into the European regional phase. Hence, in as much as the disclosure of D2 is entitled to its priority date, it is available as prior art under Article 54(3) EPC against subject matter in the opposed patent which is entitled only to its international filing date.

D2 discloses that neutrokine α (also known as ztnf4) is the ligand for TACI. This is relevant as the opposed patent is based on this allegedly novel finding.

D3 - WO 01/12812 (Biogen, Inc)

D3 has an earliest priority date of 17 August 1999 and a publication date of 22 February 2001. It duly entered into the European regional phase. Hence, in as much as the disclosure of D3 is entitled to its earliest priority date, it is available as prior art under Article 54(3) EPC against subject matter in the opposed patent which is entitled only to its international filing date.

D3 discloses that BCMA (known as BAFF-R therein) is the receptor for ztnf4 (also known as BAFF). This is relevant as the opposed patent is based on this allegedly novel finding.

D4 - WO 01/24811 (Biogen, Inc)

D4 has an earliest priority date of 6 October 1999 and a publication date of 12 April 2001. It duly entered into the European regional phase. Hence, in as much as the disclosure of D4 is entitled to its earliest priority date, it is available as prior art under Article 54(3) EPC against subject matter in the opposed patent which is entitled only to its international filing date.

D4 relates to BCMA, and is relevant to the opposed patent as claims 1 and 3 make use of soluble polypeptides comprising the extracellular domains of BCMA, as well as antibodies against BCMA. Claim 36 includes pharmaceutical compositions comprising antibodies against BCMA.

D5 - WO 98/18921 (Human Genome Sciences, Inc)

D5 was published 7 May 1998, and hence is available as full prior art against the opposed patent. D5 relates to ztnf4, which it identifies as a member of the TNF family. It is relevant, *inter alia*, because claim 3 makes use of antibodies against ztnf4.

D6 - EP 0 869 180 A1 (SmithKline Beecham Corporation)

D6 was published 7 October 1998, and so is available as full prior art against the opposed patent. D6 relates to the TNF homologue ztnf4 and is relevant for the same reasons as D5.

D7 - WO 99/12964 (Biogen, Inc)

D7 has an international filing date of 11 September 1998, and was published 18 March 1999. Hence, regardless of whether D7 is entitled to its claimed priority date, it is available as prior art under Article 54(3) EPC for the subject matter of the opposed patent entitled to priority, and as full prior art to subject matter not so entitled.

D7 relates to ztnf4 and identifies it as a member of the TNF family. It is relevant for the same reasons as D5.

D8 - WO 98/27114 (Schering Corporation)

D8 was published on 25 June 1998 and so is full prior art to the opposed patent. D8 relates to ztnf4, and is relevant for the same reasons as D5.

D9 - von Bulow et al, Science 278: 138-141, 1997

This publication is full prior art to the patent and corresponds to the patent application D1. D7 discloses the cloning of TACI, identifies the protein as a TNFR family member and analyses the structure of the protein.

D10 - Laabi et al, The EMBO Journal vol. 11 no. 11 pp. 3897-3904, 1992

This publication is full prior art to the opposed patent and discloses the cloning of BCMA, and its expression in mature B-lymphocytes.

D11 - Laabi et al, Nucleic Acids Research Vol. 22, No. 7, pp1147-1154, 1994

This publication is full prior art to the opposed patent and confirms that BCMA is preferentially expressed in lymphocyte cells undergoing B-cell differentiation.

D12 - Madry et al, International Immunology, Vol. 10, No. 11, pp 1693-1702, 1998

This publication is full prior art to the opposed patent, and identifies BCMA as a member of the TNF receptor superfamily.

D13 - Gras et al, International Immunology, Vol. 7, No. 7, pp. 1093-1106, 1995

This publication is full prior art to the opposed patent, and uses polyclonal antibodies against BCMA to demonstrate that BCMA is a non-glycosylated integral membrane protein.

The following Board of Appeal and Enlarged Board of Appeal decisions are referred to below.

G2/98 (Priority entitlement)

T0004/98 (Liposome Compositions/Sequus)

T0254/93 (Prevention of Skin Atrophy/Ortho Pharmaceutical)

T0241/95 (Serotonin Receptor/Eli Lilly)

T1046/96 (Modified Pertussis Exotoxin/Stanford)

3. The Patent

The opposed patent is concerned with two distinct alleged findings.

The first is a protein referred to as "BR43x2" which is identified as an isoform of TACI. However, this disclosure is largely unrelated to the claimed subject-matter. Only claims 29-35 primarily relate to the BR43x2 sequence. Independent claims 1, 3 and 36 are broader in scope and concern the medical use and pharmaceutical compositions that relate to the known receptors TACI and BCMA as well as BR43x2, and antibodies that are capable of binding to them.

The second is that the TNF ligand ztnf4 is a protein that binds TACI, BR43x2 and BCMA. In example 1 of the opposed patent, a secretion trap approach was used to identify BR43x2 as a receptor for ztnf4. In example 4 (not present in the priority application), TACI and BCMA-transformed cells were selected using ztnf4 binding.

Ztnf4 was known to be a TNF-related ligand before the priority date of the opposed patent (D5, D6). TACI (D1, D9) and BCMA (D10-D13) were also known, and had been identified as members of the TNF receptor superfamily.

Claims 1 and 3 of the opposed patent have apparently been formulated with the intention of reflecting the interaction between ztnf4 and BCMA and TACI (including the TACI splice variant). The claims relate to the second medical use of compounds for the manufacture of a medicament. In claim 1, the medicament is for inhibiting ztnf4 activity in a mammal. In claim 3, the medicament is for inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagement.

The list of compounds in both claim 1 and 3 includes the following:

- A polypeptide comprising the extracellular domain of BR43x2 (SEQ ID NO:2)
- A soluble polypeptide comprising the extracellular domain of TACI

- A polypeptide comprising the extracellular domain of BCMA
- A polypeptide comprising the sequence of SEQ ID NO:10 (the consensus sequence of the cysteine rich pseudorepeat found in TACI, BR43x2 and BCMA)
- An antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID NO: 2 (full-length BR43x2); SEQ ID NO:4 (a soluble form of BR43x2); SEQ ID NO:6 (full length TACI); SEQ ID NO:8 (full length BCMA) or SEQ ID NO: 10 (consensus sequence of the cysteine rich pseudorepeat)
- A polypeptide of SEQ ID NO: 4 (a soluble form of BR43x2)
- Amino acid residues 1-166 of SEQ ID NO:6 (TACI)
- Amino acid residues 8-37 of SEQ ID NO:8 (BCMA)
- Amino acid residues 1-48 of SEQ ID NO:8 (BCMA).

As discussed in more detail below, we submit that the functional definitions of the mode of action of the medicament appearing in claims 1 and 3 do not meet the requirements for an allowable second medical use claim.

Moreover, in the opposed patent as filed, page 4, line 35 to page 6, line 6 and claims 29-55 refer to a method of inhibiting BR43x2, TACI or BCMA receptor-ligand engagement, without specifying that the ligand is ztnf4. The compounds for use in this method all appear in present claims 1 and 3, and the list of disease indications corresponds to the subject matter of granted dependent claims 13-28. Similarly, page 2, lines 7-10 of the opposed patent state that the invention provides protein therapeutics for modulating the activity of ztnf4 or other BR43x2, TACI or BCMA ligands, and related compositions and methods. Hence, the applicant's own disclosure states that the claimed compounds could be expected to have an effect in the claimed disease indications, regardless of the identity of the ligand.

As well as the compounds listed above, claim 3 also includes an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID NO:18 or 20 (parts (j) and (k) of claim 3).

No mention of SEQ ID NO: 18 or 20 can be found in the description of the application as filed. However, it appears that SEQ ID NO: 18 and 20 represent the sequences of residues 22-285 of human ztnf4 and murine TACI, respectively (page 17, lines 9-10 of the application as filed erroneously refers to SEQ ID NO:19 as murine ztnf4 instead of murine TACI).

Ztnf4, also known as neutrokine α, was well known in the art at the priority date of the opposed patent. It would not be necessary to know the specific nature of the receptor to know that antibodies which bind to this ligand might inhibit its function, e.g., by blocking its binding to its receptor. That such antibodies in fact block the binding to TACI or BCMA does not represent a new effect, but only an explanation of a mechanism underlying the known use in this context.

Thus, the recitation in the claims that the medicament inhibits ztnf4 activity or inhibits BR43x2, TACI or BCMA-ztnf4 engagement adds mere information without altering either the compounds used or the nature of the downstream effect. The substance of the claims is not in fact dependent on the alleged new findings of the patent, and hence there is no real nexus between these new findings and the claims.

4. Added Subject Matter

During prosecution of the application, the patentee amended claims 1 and 3 in part (b) to require that the compound used in the use is a "soluble polypeptide comprising the extracellular domain of TACI". The aim of the amendment appears to have been to exclude the disclosure in D1 which the patentee argued only disclosed full length TACI.

The amendment was allegedly based on the application as filed as page 13, lines 18-21, page 57, lines 12-20 and page 84, lines 25-28.

Page 13, lines 18-21 merely provides a general definition that says that soluble receptor polypeptides are those which are not bound to cell membranes. There is no connection between this general statement and the subject-matter defined by the amendment to part (b) of claim 1 and 3, namely that the medical uses should employ a soluble polypeptide which comprises the extracellular domain of TACI. In short, the patentee has created a new combination of subject-matter (i.e. a new intermediate generalisation) by linking this general disclosure specifically to TACI, and so has added subject matter to the application as filed. There is no support in the application as filed for this class of polypeptides.

Further, even if it were legitimate to apply the general definition of "soluble" to TACI, the soluble definition clearly requires that the soluble polypeptide in question is a fragment of a parent, full length polypeptide, for example because it lacks a transmembrane or cytoplasmic domain so that it is not "bound to a cell membrane". On the other hand, the claim language clearly admits the possibility that soluble polypeptide is formed from a TACI extracellular domain and a further non-TACI sequence as a result of the comprising language. This clearly demonstrates that the amendment adds subject-matter over the content of the application as filed.

The other sections referred to by the patentee do not support the amendment either as in each case the solubility of TACI is disclosed in combination with other features of the polypeptides.

Page 57, lines 12-20 discloses the soluble feature in combination with the function of causing an effect on immune response.

The section referred to on page 84, lines 25-28 only supports the administration of soluble fusions of TACI to cause certain specific effects. Thus, this does not support the generalisation to the use of any type of soluble TACI protein for the uses defined in claims 1 and 3.

Additionally, during the international phase of prosecution the patentee added present claim 36. Claim 36 is directed to a pharmaceutical composition comprising an antibody or antibody fragment which specifically binds to polypeptide of SEQ ID NO: 2, 4, 6, 8, or 10, and also comprising a pharmaceutically acceptable carrier.

This claim appears to be based on references to antibodies or antibody fragments in second medical use claims 1 and 29 as filed. However, these second medical use claims only disclose the antibodies and antibody fragments in conjunction with the specific property of inhibiting ztnf4 activity, or inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagement. Claim 36 as granted, on the other hand, contains no functional limitation, and does not recite the biological property of the antibodies or fragments. Thus, it includes antibodies which, while they might bind the polypeptides in the claim, do not necessarily have the properties required in the application as filed. Hence, claim 36 is an unsupported generalisation of the content of the application as filed.

Finally, we note that the Boards of Appeal have held that the burden of proof in showing that an amendment does not add subject matter falls on the patentee and that the legal standard is beyond reasonable doubt (T1046/96). The patentee has not discharged this burden in the present case.

5. Priority Entitlement

The opposed patent claims a priority date of 7 January 1999, from US 09/226,533. However, the granted claims lack entitlement to this priority date fully or in part, for the reasons given below.

The test for priority is set out in G0002/98. In order to be entitled to priority, it is necessary that a person skilled in the art can derive the subject matter of a claim directly and unambiguously, using common general knowledge, from the previous application as a whole. The decision sets out that the concept of what constitutes the "same invention" is to be assessed strictly using the same test as is applied for the assessment of novelty and added subject matter.

The sequence identifiers in the priority application and in the opposed patent are not the same for a given polypeptide or nucleic acid. For ease of understanding, correspondence between certain polypeptide sequences is noted below:

Priority application	Granted patent	Polypeptide
SEQ ID NO:2	SEQ ID NO:2	Full length BR43x2
SEQ ID NO:4	SEQ ID NO:4	Soluble BR43x2, lacking the transmembrane and cytoplasmic domains
SEQ ID NO:8	SEQ ID NO:10	Consensus sequence of the cysteine rich pseudo repeat.
Amino acids 1-166 of SEQ ID NO:5	Amino acids 1-166 of SEQ ID NO:6	The extracellular domain of TACI
SEQ ID NO:6	SEQ ID NO:8	BCMA

Claim 1

The nearest corresponding statement to claim 1 of the opposed patent is found at page 4, lines 17-28 and page 53, lines 3-17 of the priority document.

These statements are directed to a method of inhibiting neutrokine α (ztnf4) activity in a mammal, comprising administering to said mammal an amount of a compound selected from the group consisting of:

a) a polypeptide of SEQ ID NO:4;
b) a polypeptide of SEQ ID NO:8;
c) a fusion protein;
d) a polypeptide of SEQ ID NO:5 from amino acid residue 1 to residue 166;
e) a polypeptide of SEQ ID NO:6 from amino acid residue 1 to residue 150;
f) an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID NO:4;
g) an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID NO:8.

This provides no support for the use of a polypeptide comprising any of the stated sequences, except for specific fusion proteins, discussed in more detail below. Nor does it provide support for the use of the extracellular domains of BR43x2, TACI or BCMA unless limited to the specific, recited sequences. For this reason, parts (a)-(d) of granted claim 1, which are directed to the use of any polypeptide comprising an ECD of BR43x2, TACI or BCMA or comprising the sequence of the pseudorepeat, represent a generalisation which is not entitled to the claimed priority date.

With regard to antibodies and antibody fragments, there is no support in the priority document for parts (e), (g) or (h) of claim 1 as granted. Part (e) is directed to an antibody or antibody fragment which binds specifically to any part of the full length BR43x2 sequence. The priority document only refers to antibodies and fragments which bind to the BR43x2 extracellular domain of SEQ ID NO:4. Part (g) is directed to antibodies and antibody fragments which bind to any part of the full length TACI protein, while part (h) is directed to antibodies and antibody fragments which bind to any part of the full length BCMA sequence. These embodiments are not mentioned at all in the priority application.

Parts (m) and (n) of granted claim 1 are also not entitled to the claimed priority date, because the priority document only refers to the use of a polypeptide of SEQ ID NO:6 (BCMA) from amino acid residue 1 to residue 150, and not to any smaller parts thereof.

Claim 3

Claim 3 suffers from the same deficiencies as claim 1, above. Parts (j) and (k) also find no support in the priority document, since there is no mention of the use of antibodies to ztnf4, or of SEQ ID NO:18 or 20, in the priority document.

In addition, there is no reference in the priority document to a method of inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagement.

Therefore, claim 3 lacks entitlement to priority in its entirety.

Claims dependent on claim 1 and 3 lack priority at least to the same extent as claims 1 and 3. Additional comments on certain dependent claims are provide below.

Claims 4-7

The only discussion of fusion proteins which can be used in the method of inhibiting neutrokine α activity in a mammal is found in the priority application at page 4, lines 1-9, page 4, line 28-page 5, line 4 and page 53, lines 18-23. These passages refer to fusion proteins which comprise SEQ ID NO:4 (the ECD of BR43x2), SEQ ID NO:8 (the consensus sequence of the first cysteine rich pseudo repeat), SEQ ID NO:5 from amino acid residue 1 to residue 166 (the ECD of TACI) or SEQ ID NO:6 from amino acid residue 1 to residue 150 (the ECD of BCMA).

Hence, in dependent claims 4-7, only part (a) of claim 7 is even arguably entitled to priority.

Claims 9-12

No support can be found in the priority document for a method in which the fusion protein has the features of claims 9-12.

Claims 13-28

Many of the disease indications given in dependent claims 13-28 do not find basis in the priority application.

In respect of claims 13 and 15, the priority document and the application as filed provides no basis for treatment of B-lymphocytes in general or resting B-lymphocytes. In particular, page 51, lines 9-10 of the priority document specifically states that "the ligand [ztnf4] does not act on resting B cells". This statement has been removed from the equivalent passage at page 54, line 4 of the PCT application. The only references in the priority application to the inhibition of B cells refers to activated B cells (see page 51, line 14 and page 53, lines 25-26 of the priority document).

In respect of claim 18, which depends from claims 13 and 15, multiple sclerosis is mentioned nowhere in the priority document. In respect of claims 21, which depends from claims 13 and 15, no mention can be found in the priority document of at least renal neoplasms, light chain neuropathy or amyloidosis.

At least claims 19, 20 and 22-28 appear to lack entitlement to priority in their entirety.

Claim 36

Claim 36 is directed to a pharmaceutical composition comprising an antibody or antibody fragment which specifically binds to SEQ ID NO: 2, 4, 6, 8, or 10 and a pharmaceutically acceptable carrier.

However, no mention is made in the priority document of antibodies which bind specifically to TACI or BCMA, nor to pharmaceutical compositions comprising antibodies and a pharmaceutically acceptable carrier.

Hence, claim 36 is also not entitled to priority.

6. Format of Medical Use Claims

The patent concerns two areas of subject-matter, the cloning of a splice variant of TACI called BR43x2 and the purported finding that a known protein, referred to in the patent as ztnf4 and elsewhere in the prior art as neutrokine α or BAFF, is capable of binding to two known and closely related receptors, TACI and BCMA.

However, the patentee has attempted to define the monopoly they are seeking using two independent second medical use claims 1 and 3. In both claims, there are long lists of alternative compounds that can be employed in the uses and a functional definition of the mechanism of action of the compound. In claim 1, the medicament is said to be "for inhibiting ztnf4 activity in a mammal" and in claim 3, the medicament is said to be "for inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagement".

The specific medical conditions falling within the functional definitions are only set out in dependent claims, as follows.

Claim 13 to 15 as granted recite that the medicament is for treating B lymphocytes, both activated and resting B lymphocytes.

Claim 16 as granted says that the medicament is for inhibiting antibody production, more particularly where it is associated with an autoimmune disease (claim 17) such as SLE, myasthenia gravis, multiple sclerosis or rheumatoid arthritis (claim 18). Claim 26 specifies that the autoimmune disease is insulin dependent diabetes mellitus or Crohn's disease.

Claim 19 as granted says that the medicament is used for the treatment of asthma, bronchitis, emphysema and end stage renal failure. Claim 20 further specifies that the renal disease [sic] is glomerulonephritis, vasculitis, nephritis or pyelonephritis.

Claim 20 as granted says that the medicament is for treating renal neoplasms, multiple myelomas, lymphomas, light chain neuropathy or amyloidosis.

Claim 22 as granted says that the medicament is for inhibiting effector T cells, for moderating immune response (claim 23) or comprising immunosuppression (claim 24). The immunosuppression may be associated with graft rejection, graft versus host disease, autoimmune disease or inflammation (claim 25).

Claim 27 as granted says that the medicament is for treating inflammation, for example associated with joint pain, swelling, anaemia or septic shock (claim 28).

The general issue arises as to what the prior art needs to disclose in order to anticipate the independent claims, and in particular whether the prior art documents need to disclose the mechanisms of action that are recited in the claim in place of medical conditions. On this point, we submit that the format of second medical use claims 1 and 3 is clearly contrary to those approved by the Boards of Appeal of the EPO. Consequently, the claims lack novelty if any prior art document discloses a compound falling within the list in the claims and its use for treating a specific condition falling within the functional definition, irrespective of whether the prior art document also discloses that the compound worked in treating the condition through the mechanism set out in claim 1 or claim 3.

As support for this legal position, we refer to T0004/98 (Liposome Compositions/Sequus) and T0254/93 (Prevention of Skin Atrophy/Ortho Pharmaceutical).

T0004/98 sets out the type of features that can be employed in second medical use claims to distinguish them from the prior art identifying these as:

(i) the illness or disease to be treated or the ailment to be cured.

(ii) the nature of the therapeutic compound to be used for treating or curing the disease.

(iii) the subject to be treated.

T0254/93 considered the question of whether finding the mechanism of action that underlies the use of a known medicament for treating a known condition can confer novelty on a second medical use claim that includes the mechanism as a feature. The Board in that case held that the mechanism could not confer novelty on such a claim, stating at point 4.8 that:

> "The mere explanation of an effect obtained when using a compound in a known composition, even if the effect was not known to be due to this compound in the known composition, cannot confer novelty to a known process if the skilled person was already aware of the occurrence of the desired effect."

These cases are relevant to the interpretation of claims 1 and 3 of this patent. The claims include a list of substances that constitute features of the invention capable of contributing to

the patentability of medical use claims. However, the functional features at the end of the claims are no more than stating the mechanism by which the compounds are supposed to work and consequently are not features that can confer novelty over a prior art disclosure of the same compound used in a medical context. This is discussed further in sections on novelty and inventive step below.

There is also the issue of whether the inclusion of the functional definitions of the conditions to be treated in claims 1 and 3 leads to insufficiency of disclosure.

T0241/95 (Serontonin Receptor/Eli Lilly) dealt with second medical use claims that were defined in terms of "a condition which can be improved or prevented by selective occupation of the 5-HT_{1c} receptor". This is, of course, similar to the recital "for inhibiting ztnf4 activity in a mammal" in claim 1 and "for inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagement" in claim 3.

The decision emphasised at point 3.1.1 that when the condition to be treated was formulated in this manner:

> "the skilled person must be given instructions, in the form of experimental tests or any testable criteria, allowing him to recognise which conditions fall within the functional definition and accordingly whether or not the therapeutic indication representing the heart of the invention falls within the scope of the claim."
>
> "The discovery on which the invention is based, even if representing an important piece of scientific knowledge, still needs to find a practical application in the form of a **defined, real** treatment of any pathological condition in order to make a technical contribution to the art and be considered an invention eligible for patent protection".

The Board then held that because the claim in question encompassed "an undefined number of other conditions all allegedly capable of being improved or prevented by the selective occupation of the $5HT_{1c}$ receptor" that the application in question failed to meet the requirements of Article 84 as it was not clear whether the skilled person could establish whether a particular condition fell within the scope of the functional definition of the claim. In this case, similar considerations apply under sufficiency of disclosure.

7. The Prior Art and Novelty

D1 - WO98/39361 (St Jude Children's Research Hospital)

D1 was considered during prosecution but its relevance to the claimed subject matter, and in particular the medical use claims appears to have been overlooked.

D1 discloses the cloning of Transmembrane Activated CAML Interactor (TACI) protein and identifies it as a TNFR family member. D1 further discloses therapeutic uses of TACI and related polypeptides.

The disclosure of D1 is not limited to full length TACI protein and amino acid sequences. D1 also describes the use of extracellular domains (ECD) of TACI, which may be an amino acid sequence from amino acid residues 1-166 of the N-terminal of TACI (page 7, lines 19-24 and page 18, lines 21-30), chimeric proteins comprising the TACI ECD (page 8, lines 8-15 and page 24, line 19 to page 25, line 28), and proteins encoded by nucleic acid having at least 60% sequence identity to the TACI sequence (see claim 1). Antibodies capable of binding TACI are also disclosed as having therapeutic use (page 3, lines 25-26, page 49, lines 30-32, page 58, lines 1-6).

The authors of D1 note on page 3, line 22 to page 4, line 12 that their proteins can be used in medical applications, in particular suggesting their use:

> "for lymphocyte activation of a receptor found on all B cells but only on a subset of T cells".
>
> "to specifically regulate B cell responses without affecting mature T cell activity".
>
> "where an increase or decrease of antibody production independent of cellular immune response is desired, e.g. during an infection (increase) or to avoid immune complex deposition complications (rheumatoid arthritis, glomerulonephritis, and other autoimmune conditions)".
>
> "to treat cancers of T and B cells".

Page 3, line 25 expressly mentions that:

> "the soluble, extracellular domain can be used to inhibit cellular activation".

i.e. constructs comprising the TACI ECD are useful as inhibitors by binding to the ligand of TACI.

The extracellular domain is described on page 8, lines 1-6 as being useful as a reagent, for:

> "Administration of such a polypeptide acts to suppress the immune system. Such administration is useful in the treatment or prevention of autoimmune disease or graft-rejection or graft-vs-host disease following transplantation".

There is a more detailed discussion of the medical applications of inhibiting lymphocyte function using the polypeptides of the invention. The list of conditions set out on pages 15 onwards include:

- lymphocyte mediated autoimmune disease
- transplant rejection syndrome
- graft-vs-host disease
- myelomas, lymphomas and leukemias, especially of B cells and immature T cells
- in slowing the proliferation of cancer cells
- activating lymphocytes for treating infections and anti-tumour immune responses

Furthermore, page 58, lines 8-22 discloses that TACI inhibition is useful for treating undesirable immune response including inflammatory disease, immune complex induced vasculitis, myasthenia gravis and systemic lupus erythematosus.

Therefore, we submit that the disclosure in D1 clearly discloses compounds falling within parts (b) and (g) of claims 1 and 3, namely soluble polypeptides comprising the ECD of TACI, and antibodies against the TACI sequence.

Compounds falling within part (l) of claim 1 and part (m) of claim 3, namely amino acid residues 1-166 of SEQ ID NO:6 (TACI), are also clearly disclosed in D1.

Moreover, SEQ ID NO:10 is the consensus sequence of the cysteine rich pseudorepeat which appears in at least BCMA and TACI (see page 15, lines 15-33 of the opposed patent as filed). Hence, by definition TACI must be a polypeptide comprising SEQ ID NO: 10, and compounds falling within part (d) of claims 1 and 3 are disclosed in D1.

Medical uses of these compounds falling within the scope of the claims are also disclosed in D1, as discussed further below. Therefore, claims 1 and 3 of the opposed patent are anticipated by D1 (see the discussion of the interpretation of the second medical use claims).

At least the subject-matter of claims 13 to 27 are disclosed in D1. With regard to claim 19, it is apparent that glomerulonephritis and vasculitis are examples of end stage renal failure, from the dependency of claim 19 on claim 20 and from page 55, line 29 to page 56, line 4 of the opposed patent.

Claim 2 states that the mammal in which the ztnf4 activity is inhibited in a primate. This lacks novelty over the disclosure of a human subject at page 60, line 5 of D1.

Claim 4 relates to fusion proteins consisting of a first and second portion, where the first portion comprises a polypeptide comprising (*inter alia*) amino acids 34-66, 71-104 or 25-104 of SEQ ID NO:6 (TACI), and the second portion comprises another polypeptide. Claim 5 requires that the first portion further comprises amino acid residues 105-116 of SEQ ID NO:6. Claim 6 requires that the fusion protein comprises the extracellular domain of TACI.

Page 24, lines 20-34 of D1 discloses fusions between functional fragments of TACI and another protein. Page 18, lines 21-30 of D1 discloses that one possible functional fragment of TACI is the soluble extracellular domain spanning amino acid residues 1-166. Hence, at least claims 4-6 lack novelty over D1.

Page 24, lines 24-26 of D1 states that the second polypeptide can be an Fc domain of an immunoglobulin portion of an antibody. Thus, claim 8 lacks novelty over D1.

In addition, D1 discloses antibodies capable of binding TACI (page 9, lines 5-15), their therapeutic use (page 3, lines 25-26, page 49, lines 22-32), and therapeutic compositions comprising TACI antibodies (page 58, lines 24-28). Thus, at least part (c) of claim 36 is disclosed in D1. Polyclonal, human monoclonal and humanised mouse antibodies are discussed at page 50, line 3, page 50, line 30 and page 50, line 33 to page 51, line 8 respectively. Fab fragments are mentioned at page 51, line 22 of D1. Hence, dependent claims 37 and 38 also lack novelty over D1.

D2 - WO 00/67034 (Immunex Corporation)

D2 discloses that neutrokine α (ztnf4) is the ligand for TACI (see page 4, lines 1-7 of D2 and of its priority application). Neutrokine α/ztnf4 is referred to in D2 as "TACI ligand". Hence, D2 discloses the ligand/receptor relationship which is alleged to underlie the purported invention of the opposed patent.

D2 discloses the therapeutic use of agonists and antagonists of the TACI/ztnf4 complex in the treatment of diseases modulated by the complex (page 4, lines 32-34 of D2, and page 4, lines 28-30 of the priority application). Page 9, lines 17-20 of D2 and page 9, lines 9-11 of the priority document state that the antagonist can be an antibody which binds to the binding site of TACI.

Hence, part (g) of claim 1 and claim 3 are clearly anticipated by this document. This is the case even if the functional definitions recited in claims 1 and 3 (namely, the inhibition of ztnf4 activity of BR43x2, TACI or BCMA receptor-ztnf4 engagement) are taken into account, though we submit that it would be incorrect to do so, for the reasons explained above. There is explicit disclosure in D2 that the antagonists are to inhibit TACI/ztnf4 engagement, and hence inhibit ztnf4 activity.

The therapeutic uses which are suggested for the antagonists include acute respiratory disease syndrome; tumor and tumor metastasis; autoimmune disease including multiple sclerosis and diabetes; viral infection; rheumatoid arthritis; graft reject; IgE-mediated allergic reactions; and inflammation. These diseases are mentioned in the published application at page 9, lines 32-33 and page 10, lines 3-9, and in the priority application at page 9, lines 24-25 and page 9, line 29 to page 10, line 1.

Thus, at least dependent claims 16-18 and 22-27 lack novelty over D2.

D2 also discloses that the antagonists, including an antibody which binds to the binding site of TACI, can be administered for therapy with a suitable carrier (page 12, lines 4-18 of D2 and page 11, line 26-29 of the priority application). Hence, part (c) of claim 36 is anticipated by D2. Fab fragments are disclosed at page 9, line 30 of D2 and page 9, line 22 of the priority document, and so at least dependent claim 38 also lacks novelty.

D3 - WO 01/12812 A2 (Biogen, Inc)

D3 relates to a BAFF receptor, which it calls "BAFF-R". At page 1, line 22 of D3, it is noted that BAFF-R is the same as "BCMA". The sequence given for BAFF-R in the earliest priority document of D3 is identical to the sequence given for BCMA at SEQ ID NO: 8 of the opposed patent.

BAFF is an alternative name for ztnf4 (see the opposed patent as filed, page 1 line 33- page 2 line 4). Therefore, like D2, D3 discloses the ligand/receptor relationship which is alleged to underlie the opposed patent.

The disclosure of D3 is not limited to the full-length receptor. D3 also discloses that it is possible to use a form of BCMA which is free of transmembrane and cytoplasmic domains (page 11, lines 13-14, page 11, line 33 to page 12, line 11 and page 20, lines 20-21 of D3; and page 11, lines 18-19, page 12, lines 1-12 and page 21, lines 7-8 of the earliest priority document).

Furthermore, since SEQ ID NO:10 defines a consensus sequence of a cysteine rich motif appearing in at least BCMA and TACI (page 15, lines 15-33 of the opposed patent as filed), then by definition BCMA is a polypeptide comprising SEQ ID NO: 10.

D3 further describes the use of antibodies against BCMA (see page 4, line 5 and page 13, lines 11-21 of D3, and claims 21, 27, 39, 45, 53, 68, 76, 78, 81, 83, 84 of the earliest priority document), and a chimeric protein comprising BCMA fused to a heterologous sequence (page 4, lines 9-12 and page 20, line 20 to page 21, line 5 of D3, and page 5, lines 11-14 and page 21, lines 8-24 of the earliest priority document).

D3 states that included in the methods of the invention are "methods of using agents for treating, suppressing or altering an immune response involving a signalling pathway between BAFF-R [BCMA] and its ligand" (page 3 line 33-page 4 line 1). Page 11, lines 13-14 states that "the claimed invention includes in certain embodiments methods of using peptides derived from BAFF-R [BCMA] which have the ability to bind BAFF [ztnf4]". Hence, there is

disclosure in D3 that the methods of the invention will block BCMA-ztnf4 engagement and so inhibit ztnf4 activity.

Compounds which fall within parts (c), (d) and (h) of claims 1 and 3 are clearly disclosed in D3. Hence, claims 1 and 3 lack novelty over D3, even if the functional definitions recited in claims 1 and 3 (namely, the inhibition of ztnf4 activity or BR43x2, TACI or BCMA receptor-ztnf4 engagement) are taken into account, though we submit that it would be incorrect to do so.

D3 describes the therapeutic use of the BCMA and BCMA-related molecules for inhibiting B-cell growth, dendritic cell-induced B-cell growth and maturation or immunoglobulin production in an animal (page 3, lines 21-24 of D3, page 4, line 30 to page 5, line 2 of the priority document). It also discloses treatment of autoimmune diseases, hypertension, cardiovascular disorders, renal disorders, B-cell lympho-proliferative disorders, immunosuppressive diseases, organ transplantation and HIV (page 3, lines 30-33 of D3, page 5, lines 1-6 of the earliest priority document).

Furthermore, D3 states that:

> "The invention relates to use of BAFF-R and BAFF-R related molecules to effect the growth and maturation of B cells and the secretion of immunoglobulin. The invention relates to use of BAFF-R and BAFF-R related molecules to effect responses of the immune system, as necessitated by immune related disorders. Additionally, this invention encompasses the treatment of cancer and immune disorders through the use of a BAFF-R, or BAFF-R related gene through gene therapy methods.
>
> "The BAFF-R and homologs thereof produced by hosts transformed with sequences of the invention, as well as native BAFF-R purified by the processes known in the art, or produced from known amino acid sequences, are useful in a variety of methods for anticancer, antitumor and immunoregulatory applications." (Page 10, lines 4-14 of D3 and page 10, lines 9-18 of its earliest priority document).

The disclosure of compounds which are included in claims 1 and 3 and medical uses of the compounds falling within the scope of the dependent claims also shows that claims 1 and 3 lack novelty over D3.

At least dependent claims 13, 16, 17 and 22-25 lack novelty over the disclosure of this document, as dependent on each of parts (c), (d) and (h) of claims 1 or 3. D3 also discloses the use of antibodies against BCMA to inhibit inflammation (page 4, lines 1-2 of D3 and claim 65 of the priority application). Therefore, claim 27 as dependent on part (h) of claim 1 or 3 also lacks novelty over D3.

Page 20, line 20 to page 21, line 2 of D3 describe a receptor inhibitor comprising an extracellular domain of BCMA fused to a human Fc domain. This is supported in the earliest priority document at page 21, lines 7-22. Hence, at least dependent claims 4-6 and 8 and 9 lack novelty over D3.

With regard to claim 36, D3 discloses antibodies against BCMA and their use in treatment as discussed above, and hence at least part (d) lacks novelty over this document. Page 13, lines 18-19 of D3 and page 13, lines 13-14 of the earliest priority document disclose that the antibody can be monoclonal or polyclonal, and so at least claim 37 also lacks novelty.

D4 - WO 01/24811 (Biogen, Inc)

D4 is related to BCMA, which is stated to be a receptor for the tumour necrosis factor, APRIL (see page 4, lines 10-11 of D4 and page 4, lines 20-21 of D4's earliest priority application). In D4, BCMA is also referred to as "APRIL-R".

As well as full-length BCMA, D4 relates to a soluble form of BCMA lacking the transmembrane and cytoplasmic domains. This is disclosed in D4 at page 12, lines 23-24, page 13, lines 4-5, page 16, line 26-27 and page 27, lines 22-30. It finds basis in the earliest priority document at page 13, lines 4-15, and page 22, lines 3-4.

D4 discloses the use of BCMA (APRIL-R) and BCMA related molecules to affect the growth and maturation of B-cells, specifically as they relate to tumour cells. D4 also relates to the use of BCMA and BCMA related molecules to effect responses of the immune system, as necessitated by immune related disorders. Hence, the document relates to the use of BCMA and BCMA related molecules to treat cancer and immune disorders, and in immunoregulatory applications. This is disclosed in D4 at page 11, lines 14-25 of D4, and finds basis in the earliest priority document at page 11, lines 8-20.

D4 also states that the invention provides methods of inhibiting B-cell and non-B cell growth, dendritic cell-induced B-cell growth and maturation or immunoglobulin production in an animal using BCMA peptide. In addition, D4 describes methods of using BCMA in the treatment of autoimmune diseases, hypertension, cardiovascular disorders, renal disorders, B-cell lympho-proliferative disorders, immunosuppressive disorders, organ transplantation, inflammation and HIV (page 22, lines 5-13 of D4 and page 16, lines 15-21 of the earliest priority document).

Thus, parts (c) and (d) of claims 1 and 3 lacks novelty over D4 (BCMA being a polypeptide which comprises a sequence falling within SEQ ID NO:10, as explained above).

At least dependent claims 13, 16, 17, 22-25 and 27 also lack novelty over this document based on the therapeutic indications mentioned in D4.

D4 also discloses the use of anti-BCMA antibodies in the treatment of cancer (page 4, lines 17-31 of D4 and page 4, line 27 to page 5, line 10 of the earliest priority document) and in the treatment of conditions associated with undesired cell proliferation (claim 1 of D4 and claim 16 and claim 19 of the earliest priority document). Hence, part (g) of claims 1 and 3 also lack novelty over this document.

Moreover, part (d) of claim 36 of the opposed patent lacks novelty over the disclosure of BCMA antibodies, their use in therapeutic methods, and their formulation into a pharmaceutical composition, as discussed above. Antibodies which are monoclonal, polyclonal or humanized are described (page 14, line 16-19 and line 27 of D4, and page 14, lines 16-19 and line 27 of its earliest priority document), and so at least claim 37 also lacks novelty over D4.

D5-D8, discussed below, are relevant for the assessment of novelty of part (j) of claim 3 of the opposed patent.

D5 - WO98/18921 (Human Genome Sciences, Inc)

D5 discloses the amino acid sequence of neutrokine α, also known as ztnf4 (SEQ ID NO:2). D5 also discloses antibodies against neutrokine α (page 10, lines 25-27, page 45, line 27 to page 48, line 12) which are useful in methods of therapy (page 11, lines 1-2, page 13, lines

8-13, page 56, line 15 to page 57, line 28), for example as preferred antagonists of neutrokine α.

Therapeutic applications for antagonists of neutrokine α mentioned in D5 include the inhibition of B-lymphocytes and T-cell subsets such as activated and CD8 cytotoxic T-cells and natural killer cells, in certain autoimmune and chronic inflammatory diseases (page 56, lines 15-19). Examples of specific conditions include multiple sclerosis and insulin dependent diabetes (page 56, line 20), asthma (page 57, line 4) and rheumatoid arthritis (page 57, lines 10).

Hence, at least part (j) of claim 3 and dependent claims 13, 16-19 and 20-27 lack novelty over D5.

D6 - EP 0 869 180 A1 (SmithKline Beecham Corporation)

D6 concerns a TNF homologue which it calls TL5. This is an alternative name for neutrokine α and ztnf4, as confirmed by WO 00/67034 (D2), page 3, lines 3-12. The sequence of human TL5 is disclosed in table 2b.

Antibodies against TL5 are disclosed at page 12, lines 9-27 of D6. At page 12, lines 24-27, the document states:

> "Antibodies against TL5 polypeptides may also be employed to treat chronic and acute inflammation, arthritis, septicaemia, autoimmune disease (e.g., inflammatory bowel disease, psoriasis), transplant rejection, graft vs. host disease, infection, stroke, ischemia, acute respiratory disease syndrome, restenosis, brain injury, AIDS, bone diseases, cancer (e.g., lymphoproliferative disorders), atherosclesois, and Alzheimers disease, among others."

Hence, at least part (j) of claim 3, and dependent claims 16-18, 22-25 and 27 lack novelty over D6.

D7 - WO 99/12964 (Biogen, Inc)

D7 discloses a TNF family member which it calls "Kay-ligand". The sequence given for Kay-ligand in SEQ ID NO:2 of D7 is the same as the sequence of ztnf4, e.g., shown in D5.

Antibodies against ztnf4 are disclosed at page 7, lines 5-7 and page 14, line 21 to page 16, line 23, and it is stated that these antibodies can be used in the treatment of cancers and in the manipulation of the immune system to treat immunological diseases.

It is also stated that "the Kay-ligand [ztnf4] is present primarily in the spleen and in peripheral blood lymphocytes, strongly indicating a regulatory role in the immune system" (page 13 lines 13-14 of D7).

Hence, at least part (j) of claim 3, and dependent claims 16,17 and 22-24 lack novelty over D7.

D8 - WO 98/27114 (Schering Corporation)

D8 discloses a TNF ligand family member, which it designates 63954. The sequences given in the application correspond to the sequence of ztnf4 (see for example SEQ ID NO:4 of D8).

Antibodies which specifically bind to a 63954 protein or peptide are disclosed at page 5, lines 1-23 of D8. At page 7, line 35 to page 8 line 5, it is stated that:

> "Another method provided is treating an organism having an abnormal immune response by administering to said organism an effective dose of: an antibody or binding partner which binds specifically to a 63954; a substantially pure 63954 protein, or a peptide thereof; or a nucleic acid encoding a 63954 peptide. The abnormal immune response may be characterised by a T cell immune deficiency; chronic inflammation; or tissue rejection".

Page 38, lines 10-18 state that:

> "Antagonists of 63954, such as the naturally occurring secreted form of 63954 or blocking antibodies, may also be useful. They may provide a selective and powerful way to modulate immune responses in abnormal situations, e.g., autoimmune disorders, including rheumatoid arthritis; systemic lupus erythematosis (SLE), Hashimoto's autoimmune thyroiditis, as well as acute and chronic inflammatory responses in which T cell activation, expansion and/or immunological T cell memory plays an important role".

The use of antibodies in treating cancerous or degenerative conditions is also mentioned at page 37, lines 15-22.

Thus, at least part (j) of claim 3 and dependent claims 16-18, 22-25 and 27 lack novelty over D8.

D13 - Gras et al, (1995)

D13 discloses polyclonal antibodies specific to BCMA, and compositions containing said antibodies. Page 1094, second column describes the affinity purification of anti-BCMA antibodies. It is stated that:

> "The purified antibodies were concentrated 10-fold, dialyzed against PBS and stored in 50% glycerol at -20°C".

Claim 36 of the opposed patent is directed to a pharmaceutical composition comprising an antibody or antibody fragment which specifically binds to SEQ ID NO:8 (BCMA), an a pharmaceutically acceptable carrier.

This product claim must be interpreted as including any composition which is suitable for pharmaceutical use and which includes a pharmaceutically acceptable carrier, even if said use is not disclosed.

The composition of BCMA antibodies described in D13 would be inherently suitable for pharmaceutical application. Glycerol a solvent or vehicle that is suitable for use in and is used in pharmaceutical applications. Therefore, claim 36 lacks novelty over this document.

8. Inventive Step

It is submitted that the subject matter claimed in the opposed patent, in as much as it is novel, lacks inventive step.

The association of ztnf4 and TACI, BCMA or BR43x2

The opposed patent is based on the observation that the ztnf4 ligand binds to BR43x2 and also to TACI and BCMA.

In example 1 of the opposed patent, a secretion trap approach was used to identify BR43x2 as a protein that binds ztnf4. In example 4, TACI and BCMA-transformed cells were selected using ztnf4 binding.

TACI and BCMA were also known at the priority date of the opposed patent. Both D1 and D9 disclose the cloning of TACI, identify the protein as a TNFR family member and analyse the structure of the protein.

D10 and D11 discuss the earlier cloning of the BCMA gene, and D12 identifies it as a member of the TNFR superfamily.

As explained above, D1 further suggests that TACI, soluble forms of TACI and antibodies against TACI can be used in methods of therapy, which include methods of the dependent claims of the opposed patent. Antibodies useful in antagonising TACI are said to block access to TACI in lymphocytes (page 49 lines 30-31). Similarly, the extracellular domain of TACI is stated to function as a dominant negative or blocking reagent, which intercepts the endogenous normal ligand (page 8 lines 1-4). Hence, the skilled person would be well aware that antibodies against TACI and extracellular portions of TACI would block ligand binding to the receptor and hence prevent the ligand activity.

As discussed above, it is submitted that the functional definitions of the purpose of the medicament in claims 1 and 3 (namely, the inhibition of ztnf4 activity or the inhibition of BR43x2, TACI or BCMA receptor-ztnf4 engagement) cannot bestow novelty on the claim, as they do not define a disease condition, still less a disease condition distinct from those known in the art to be treatable with the listed compounds. Accordingly, no technical problem is solved by the identification of the ligand in the context of the claim.

With respect to part (j) of claim 3, the position is similar. Ztnf4 was known at the priority date of the opposed patent, and had also been identified as a TNF ligand in D5-D8. The inhibition of ztnf4 using antibodies against ztnf4 is known from D5-D8, above.

Hence, claims 1 and 3 lack inventive step over the disclosure of D1.

Medical Indications and Pharmaceutical Compositions

Claims 13-28 relate to disease indications for the medicament of claims 1 and 3. As noted above, many of these are known from the prior art. Those indications which are not explicitly disclosed, however, lack inventive step over D1.

D1 explicitly discloses the use of compounds according to the opposed patent in the treatment of, *inter alia*, autoimmune diseases, inflammation and myelomas, lymphomas and leukemias (e.g., page 16 lines 25-31; page 58 lines 1-23). Well known examples of autoimmune diseases, inflammatory diseases and myelomas, lymphomas and leukemias therefore represent mere alternatives to the conditions disclosed in D1, and lack inventive step without unexpected benefits.

Moreover, it is clear from the opposed patent that the list of conditions has been derived from consideration of the specificity of the ligand and receptor for B cells.

Page 53 lines 27-34 of the opposed patent (as filed) state:

> "Therefore, the specificity for B cells by the ligand and receptor suggests that they are useful for the study and treatment of autoimmunity, B cell cancers, immunomodulation, IBD and any antibody mediated pathologies, e.g., ITCP, myasthenia gravis and the like, renal disease, indirect T cell immune response, graft rejection, graft versus host disease." (Emphasis added).

The opposed patent also states that ztnf4 has been shown to activate B cells resulting in B cell proliferation, antibody production and up-regulation of activation markers *in vitro* (page 53 lines 35-38). Again, this association with B cell activity has lead to the suggestion of utility in B-cell associated disorders:

> "Thus, the polypeptides of the current invention can be targeted to specifically regulate B cell responses, inhibiting activated B cells, during the immune response, without inhibiting other cell populations which is advantageous during the treatment of disease. Additionally, the polypeptides if the present invention could be used to modulate B cell development, development of other cells, antibody production and cytokine production" (page 54, lines 6-13 of the opposed patent as filed).

It is apparent from these statements that the therapeutic indications described in the opposed patent are derivable from the fact that the ligand and receptor are B-cell specific.

However, TACI was already known to be specific to B cells. D9 reports Northern blot data on page 138, middle column showing that TACI mRNA is expressed "in spleen, small intestine, thymus and peripheral blood lymphocytes, suggesting that a single TACI transcript is present in both T and B lymphocytes". A polyclonal antibody to TACI was used to demonstrate its presence on the surface of B cells, but not resting T cells (page 138, right hand column).

D1, page 3, lines 31 to page 4, line 3 states that:

> "A particular advantage of the present invention is that it provides lymphocyte activation of a receptor found on all B cells, but only on a subset of T cells. The receptor can thus be targeted to specifically regulate B cell responses without affecting mature T cell activity. Such targeting specificity is always advantageous, particularly where an increase or decrease of antibody production independent of cellular immune response is desired, e.g., during an infection (increase) or to avoid immune complex deposition complications (rheumatoid arthritis, glomerulonephritis, and other autoimmune conditions)".

The conditions listed in the opposed patent would have been produced generally by the person skilled in the art based on the known specificity of TACI. Indeed, it largely was so produced by the authors of D1.

Thus, the derivation of the conditions claimed in the opposed patent is not dependent on the identification of ztnf4 as the ligand for the receptors, and the claims relating to specific disease indications lack inventive step.

BCMA and its Use in Medical Indications and Pharmaceutical Compositions

BCMA was also known at the priority date of the opposed patent. It was known to be a member of the TNFR family and was also known to have a specific role in the maturation of B-cells.

D10 discloses the sequence of BCMA (figure 8). It also discloses that BCMA RNA is expressed mainly, if not only, in mature B cells: indeed, BCM stands for "B cell maturation" (page 3901, right hand column). In view of the expression data, a role for BCMA in lymphoid proliferation and/or differentiation was postulated (page 3902, first paragraph of discussion section).

D11 confirms that BCMA RNA is found mainly in lymphoid cells undergoing B cell differentiation (right hand column of page 1147, lines 26-28). The document states that:

> "RNase protection assays clearly confirmed that the BCMA gene is preferentially expressed in the B-cell lineage. The BCMA gene is not expressed in the T-cell lines tested (except the SUPT11 post thymic T-cell line) and not at all in the myeloid cell lines used in this study" (page 1152, third paragraph of the discussion).

D12 identifies consensus sequences from the human and mouse BCMA, and identified six cysteine residues that are conserved in the N-terminal part of the human and mouse proteins. This resulted in the identification of BCMA as a TNF receptor with a single cysteine motif (page 1694, paragraph bridging first and second column).

Accordingly, in consideration of the B-cell specificity of BCMA and its apparent role in B-cell maturation, the skilled person would have proposed that the downregulation of BCMA would be effective in treating B-cell mediated diseases such as those associated with antibody activity, and hence would have proposed conditions currently claimed in the opposed patent.

Antibodies against BCMA and soluble, ligand sequestering fragments of BCMA would readily occur to the skilled person as methods of downregulating BCMA activity. In respect of the inhibition of a transmembrane receptor, the use of antibodies and the receptor extracellular domain are used often in the art.

Parts (c) and (h) of claims 1 and 3, which relate to use of the extracellular domain of BCMA and to antibodies specific to BCMA, therefore not only lack novelty in respect of D5 and D6, but also lack inventive step in consideration of D10 to D12 in combination with D1. This applies equally to claims dependent on parts (c) and (h) of claims 1 and 3, and to part (d) of claim 36.

Parts (m) of claim 1 and (n) of claim 3 relate to the use of amino acid residues 8-37 of SEQ ID NO:8 (BCMA) in the manufacture of a medicament. Parts (n) of claim 1 and (o) of claim 3 relate to the use of amino acid residues 1-48 of SEQ ID NO:8 (BCMA) in the manufacture of a medicament.

It is unclear if these parts of the claim are closed or open definitions. If they are open definitions, i.e., relate to polypeptides comprising amino acid residues 8-37 or 1-48, then they lack novelty over D3 and D4 for the same reason as the use of a polypeptide comprising the BCMA extracellular domain. If the definitions are intended to be closed, that is, to relate to polypeptides consisting of amino acid residues 8-37 or 1-48, then the opposed patent does not indicate any problem solved by these specific fragments as compared to the ECD as a whole. Thus, these parts of the claims lack inventive step to the same extent as use of the BCMA ECD.

BR43x2

In the opposed patent, BR43x2 is identified as an isoform of the known protein TACI. Claims 1 and 3 include the use of an extracellular domain of BR43x2 or an antibody directed to BR43x2 in the manufacture of a medicament for inhibiting ztnf4 activity in a mammal, or inhibiting BR43x2, TACI or BCMA-ztnf4 engagement (parts (a), (e), (f), and (k) of claim 1,

and parts (a), (e), (f), and (l) of claim 3). Claims 29-35 are directed to the BR43x2 polypeptide and nucleic acids, and to vectors and cultured cells comprising the nucleic acid.

As shown in figure 1 of the opposed patent, BR43x2 is identical almost in full to TACI, but lacks the first cysteine repeat motif. The skilled person would be aware that alternative splice products are common in members of the TNFR superfamily (see for example D12, penultimate paragraph).

D1 relates to TACI proteins and nucleotide sequences in general, and not simply to the sequences disclosed in that document. Indeed, claim 1 of D1 relates to nucleic acids having at least 60% similarity with the coding sequence of SEQ ID NO:1. The nucleic acid sequence encoding the BR43x2 variant has approximately 84% nucleotide identity to the nucleic acid sequence encoding TACI, and so is encompassed in the disclosure of D1.

Moreover, page 31, line 13 to page 33, line 6 of D1 discloses methods of identifying naturally occurring TACI variants from cDNA or mRNA. For example, it is suggested that probes against TACI could be used to screen a thymic cDNA library, since lymphocyte cells seem to have the highest expression of TACI (page 31, lines 19-23). Methods of mRNA selection are also disclosed, for example using immobilised antibodies specific to TACI (page 32, line 30 to page 33, line 6).

The opposed patent discloses that BR43x2, TACI and BCMA are expressed predominantly in the spleen and thymus (page 17, lines 9-12). Therefore, screening a cDNA library or mRNA derived from such cells using nucleic acid probes or antibodies based on the sequences disclosed in D1, the skilled person would have identified the BR43x2 splice variant.

In any case, BR43x2 is a mere sequence variant of TACI, which appears to possess no surprising function or property sufficient to support inventive step. In the opposed patent, the uses proposed for BR43x2 are identical to those disclosed for TACI. In the absence of any new effect of the sequence variant, the only problem which can be said to be solved by BR43x2 is the provision of a mere alternative sequence. The solution in the opposed patent is provide a sequence identical to the previous TACI sequence except for the deletion of one region. We submit that in this case, the BR43x2 variant, possessing no new technical effect, cannot provide inventive step.

Those medical uses which have been disclosed or are apparent for TACI, its ECD or antibodies to TACI would be equally obvious to the skilled person in connection with the TACI isoform, in the absence of any new effect associated with that isoform.

Hence, parts (a), (e), (f) and (k) of claim 1, and parts (a), (e), (f) and (l) of claim 3 lack inventive step over D1, as do claims 29-35 of the opposed patent. Dependent claims relating to use of the ECD of BR43x2 in a fusion protein, or to specific medical uses of BR43x2, lack inventive step in view of D1. Since all dependent claims lack either novelty or inventive step in respect of TACI, they lack inventive step equally in respect of BR43x2.

Parts (a) and (b) of claim 36 and the claims dependent thereon, lack inventive step for the same reason.

Moreover, due to the identity of the sequences in all respects except for the missing pseudorepeat in BR43x2, all antibodies which bind to BR43x2 will also bind to TACI, and conversely, almost all antibodies which bind to TACI will also bind to BR43x2. No improvement is shown or suggested. Thus, there can be no inventive step in using an antibody which binds to BR43x2 in a method of claim 1 or claim 3, or in the pharmaceutical

composition of claim 36, since this antibody must be an antibody which binds to TACI and this is taught in D1.

Other Matters

Claims 1 and 3 refer to the second medical use of an antibody which binds to SEQ ID NO:10 (the consensus sequences of the cysteine rich pseudorepeat). Claim 36 is directed to a pharmaceutical composition which comprises an antibody, including an antibody which specifically binds to SEQ ID NO:10. SEQ ID NO: 10 is found in TACI, for example. The opposed patent does not state what problem an antibody which binds to this sequence solves, when compared to an antibody which binds to other parts of TACI. Hence, this must be considered as merely an embodiment of the disclosure of antibodies in D1, and to lack inventive step over that document.

Claim 3 part (k) refers to the use, in the manufacture of a medicament for inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagement, of an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID NO:20. As noted above, SEQ ID NO: 20 appears to be the sequence of murine TACI. However, antibodies against TACI are taught in the treatment of disease conditions which are given in the dependent claims (D1). D1 gives the human TACI sequence. However, there cannot be any inventive step in using antibodies against the murine sequence as an alternative to this, particularly as D1 mentions that homologs from other species are included in the invention (page 16 lines 5-7, page 31 lines 18-19, page 33 lines 13-15).

Claim 7 part (b) relates to a fusion protein in which the first portion is amino acid residues 1-154 of SEQ ID NO:6 (TACI). It is unclear whether this is intended to be an open or a closed definition, i.e., if longer first portions could be included. If the definition is open, then this lacks novelty over D1 for the same reason as the TACI ECD. If a closed definition, then no indication is given in the opposed patent as to what problem is solved by the use of this fragment as compared to the complete TACI ECD. Hence, since no technical problem appears to be solved compared to D1, this claim lacks inventive step.

Claims 9-12 give further specifics as to the nature of the fusion protein and particularly, the immunoglobulin heavy chain constant region. Page 24, lines 24-26 of D1 state that the second polypeptide can be an Fc domain of an immunoglobulin portion of an antibody. Claims 9-12 simply provide routine variants of this, which would be well known to the skilled person and cannot provide inventive step.

9. Sufficiency

Claims 1 and 3 define medical conditions with reference to a mechanism of action. In claim 1, the medicament is said to be "for inhibiting ztnf4 activity in a mammal" and in claim 3, the medicament is said to be "for inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagement". Examples of specific medical conditions falling within the functional definitions are only set out in dependent claims.

As discussed in more detail under section 6 above, T0241/95 (Serontonin Receptor/Eli Lilly) stated that when the method of treatment is define only in terms of mechanism, the skilled person must be given instructions, in the form of experimental tests or any testable criteria, allowing him to recognise which conditions fall within the functional definition and accordingly whether or not a therapeutic indication falls within the scope of the claim. In the present opposed patent, no experimental test is provided. Although certain effects of ztnf4 on cells and on animals are shown in the examples, without more specific disclosure they are not sufficient to enable the skilled person to be confident that these are the only effects mediated by ztnf4 or that a disease in which the same symptoms appear is necessarily a condition

which is treatable by zntf4 inhibition. The examples also show that ztnf4 is upregulated in mice with certain disease conditions, but the claims are not limited to those conditions in which ztnf4 is upregulated. The skilled person is therefore not taught what test is to be performed.

The opposed patent indicates the diseases in which it expects ztnf4 to be useful are those which are B-cell related, such as antibody mediated pathologies and B-cell cancers, due to the specificity of ztnf4 and its receptors for B cells (page 53, lines 27-34).

As discussed above, in as much as a disease or condition could be recognised to be associated with B-cell activity or antibody function, then this condition would have been obvious to the skilled person based on the prior art. In as much as a condition is not so recognised by the skilled person, then the application is not sufficient to allow the skilled person to ascertain in advance whether that disease is one which can be treated by ztnf4 inhibition or by inhibition of BR43x2, TACI or BCMA receptor-ztnf4 engagement.

10. Conclusions

In view of the above comments, revocation of the patent in its entirety is requested.

Christopher Denison
for Simon Kiddle
Authorised Representative
MEWBURN ELLIS LLP

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Mewburn Ellis LLP

European Patent Attorneys
European Trade Mark Attorneys
European Design Attorneys
Chartered Patent Attorneys

York House
23 Kingsway
London WC2B 6HP

Tel +44 (0)20 7240 4405
Fax +44 (0)20 7240 9339
mail@mewburn.com

www.mewburn.com

DATE: 10 June 2004
TO: -
COMPANY: EUROPEAN PATENT OFFICE - MUNICH
FAX NO: -
YOUR REF: OPPOSITION TO EP 1 141 274 B
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SENDER: CHRISTOPHER DENISON
E-MAIL: chris.denison@mewburn.com
Number of pages (including this one): 25
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